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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,780	02/10/2004	Matthew J. During	106604-7	3635

21125 7590 12/17/2008

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
12/17/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/776,780	DURING, MATTHEW J.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,7-12 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,7-12 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed July 7, 2008 (hereinafter referred to as "the response") has been entered. Claims 1, 2, 11, and 12 have been amended and Claims 5 and 6 have been cancelled.

Accordingly, Claims 1, 2, 4, 7-12, and 14 remain pending in the instant application.

The objection to Claims 2, 5, 6, and 10 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, is withdrawn in view of the cancellation of Claims 5 and 6 and in view of the amendment to Claim 1.

The objection to Claims 1, 2, 4-12, and 14 pertaining to "a pharmaceutical acceptable carrier" is withdrawn in view of the amendments to Claims 1, 11, and 12 to now recite "a pharmaceutically-acceptable carrier."

The double patenting warning under 37 CFR 1.75, pertaining to Claim 12, is withdrawn in view of the amendments to Claims 11 and 12.

The objection to the drawings is withdrawn in view of the re-labeling of Figure 4A to Figure 4.

The objection to the specification is withdrawn in view of the amendment to page 67 of the specification.

The rejection of Claims 11, 12, and 14 under 35 U.S.C. 112, second paragraph, for indefiniteness in their recitation of "decreased cognition," is withdrawn in view of the amendments to Claims 11 and 12.

The rejection of Claim 11 under 35 U.S.C. 112, second paragraph, as indefinite in its recitation of "modulating or delaying onset of epilepsy, stroke, or decreased cognition" in the preamble because the body of the claim only requires administration of a composition and does not require that the stated goal of the preamble be achieved, is withdrawn in view of the amendments to Claim 11.

The rejection of Claims 12 and 14 under 35 U.S.C. 112, second paragraph, as indefinite in their recitation of "ameliorating or delaying onset of epilepsy, stroke, or decreased cognition" in the preamble and to "modify the function of an NMDA receptor" in the conclusion because the preamble claim language conflicts with the conclusory claim language, is withdrawn in view of the amendment to Claim 12.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) and 120 is acknowledged. However, the provisional applications and parent application upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for Claims 1, 2, 4-12, and 14 of this application, for the same reasons discussed hereinbelow as applied to the present application. Application serial nos. 60/116,748, 60/127,142, and parent application no. 09/491,896 fail to provide an enabling disclosure for the invention now being claimed in Claims 1, 2, 4-12, and 14, for the reasons discussed herein below as a rejection under 35 U.S.C. 112, first paragraph, as applied to the instant application.

Thus, the earlier-filed applications do not meet the requirements under 35 U.S.C. 119(e) and 120 for the benefit of obtaining priority to an earlier-filed application.

Accordingly, the Lissin et al. (June 1998) reference is applied as a 102(b)-type reference.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 7-12, and 14 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record set forth in the Office Actions of 11/21/05 and 11/30/06 and for the reasons set forth below,

because the specification, while being enabling for (i) a composition comprising an AAV vector comprising a nucleic acid encoding NMDAR1 operably linked to a promoter and (ii) a method of ameliorating brain damage associated with epilepsy or stroke in a rat, via prior oral administration of said AAV vector, such that the antigen is expressed and elicits production of NMDAR1-specific antibodies in the circulatory system of the rat, wherein epileptic seizures are diminished and stroke infarct volume is decreased as compared to an untreated control rat, does not reasonably provide enablement for a composition comprising any vector encoding any NMDA receptor antigen, nor for a method of modulating or delaying onset of epilepsy, stroke, or decreased cognition in any subject, by administration of any vector encoding any NMDA receptor antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of enablement set forth above is not intended to suggest specific claim language, but rather is intended to advise Applicant of the broadest scope that is considered to be enabled. It is Applicant's responsibility to identify claim language that is properly supported in the specification and that falls within the scope acknowledged to be enabled.

At pages 10-11 of the response, Applicant asserts that autoantibodies cross the blood-brain barrier (BBB) when the BBB is compromised due to disease or injury. Applicant further asserts that the claims as amended are enabled because of this, and that one of ordinary skill in the art would recognize that the claimed invention is useful for the recited disorders and the skilled artisan can "make and use" the claimed invention without any undue experimentation. Applicant further alleges that clinical data is not necessary for patentability. However, the capability of circulating antibodies to cross the BBB barrier does not address the unpredictability inherent to the art of DNA vaccination. Furthermore, the instant specification does not provide specific guidance teaching which conditions will sufficiently compromise the BBB to the extent that sufficient amounts of antibodies are able to cross and produce the desired

effect. As regards clinical data, there is nothing in the rejection that requires clinical data. The claimed invention recites claim-designated effects that must be enabled by the specification. Applicant goes on to claim that *in vivo* or clinical data is not necessary for patentability analysis. However, there is nothing in the enablement rejection suggesting that *in vivo* or clinical data is required. A complete *Wands* analysis has been provided, with a discussion of those factors most relevant to the present claims, including the nature of the invention, the state of the prior art, the predictability of the art, the breadth of the claims, the amount of direction or guidance presented, the presence or absence of working examples, and the quantity of experimentation necessary to enable the claims over their full scope. Giving due consideration to all the *Wands* factors, it was concluded that the specification fails to provide an enabling disclosure for the full scope of the claims. Numerous references were provided pointing to the unpredictability in the art of DNA vaccination and it is maintained that the specification fails to enable the full scope of the claims.

Given the *Wands* analysis of record, the specification fails to enable the full scope of the claims. The court has stated that "[n]aturally, the specification must teach those of skill in the art how to make and use the invention as broadly as it is claimed." *In re Goodman*, 29 USPQ2d 2010 at 2013 (Fed. Cir. 1993).

The unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman,* 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991).

Thus, it is maintained that the specification fails to enable the full scope of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 7, 8, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lissin et al. (June 1998) in view of Kammesheidt et al. (1996).

Lissin et al. (June 1998) disclose an adenovirus that encodes an NMDA receptor (NR1), which is capable of being expressed in cultured hippocampal neurons (abstract; page 7098, column 1, paragraphs 2-3; and Figure 1). Thus, the reference teaches all the limitations of the claims as written, with the exception of a pharmaceutical carrier. However, Lissin does expressly teach that important issues for future work include elucidating the NMDAR-dependent signal transduction cascade that is responsible for the decrease in the surface expression of AMPAR clusters at synapses and determining under what conditions these changes occur *in vivo*. (page 7102, sentence bridging columns 1 and 2) Accordingly, Lissin provides the explicit motivation to express epitope-tagged NMDA receptors (HA-NR1) *in vivo* for studying the conditions under which these changes in receptor surface expression occur *in vivo*. Thus, one of skill in the art would have resuspended the recombinant adenovirus in a pharmaceutical carrier suitable for *in vivo* administration, such as sterile saline. The recombinant adenovirus could then be administered *in vivo* to the rat hippocampus to study the surface expression of the epitope-tagged NMDA receptor at synapses under varying conditions, particularly examining the effects of manipulating neuronal activity on the surface expression of this receptor.

Kammesheidt et al. (1996) disclose the use of recombinant adenoviruses to transduce rat hippocampal cells *in vivo*. A recombinant adenovirus comprising the β-galactosidase gene under control of the cytomegalovirus (CMV) promoter was constructed, purified by cesium chloride banding, and

resuspended in phosphate-buffered saline (PBS) for stereotactic injection into the rat hippocampus to transduce CA1 neurons (sections 2.1 and 2.2). The study demonstrated that efficient widespread transduction of CA1 *in vivo* was rapidly achievable and was sustained for more than 5 weeks (abstract and page 301, column 2, paragraph 2). The authors conclude that "the adenoviral system can be applied to specific modulations of hippocampal proteins *in vivo* and in studying mechanisms of synaptic plasticity such as LTP and LTD" (page 304, column 1, paragraph 4). Thus, the reference shows that adenoviral vectors are useful for *in vivo* gene transfer into the rat hippocampus.

Since Lissin provides the explicit motivation to express epitope-tagged NMDA receptors *in vivo* for studying the conditions under which synaptic changes occur *in vivo*, the skilled artisan would have been motivated to take the HA-NR1 recombinant adenovirus of Lissin, purify it, and resuspend it in sterile saline as taught by Kammesheidt for *in vivo* administration into the rat hippocampus. This would have allowed the skilled artisan to study the *in vivo* effect of neuronal activity on the regulation of surface expression of NMDA receptors. The skilled artisan would have compared the *in vivo* effects with the results obtained *in vitro* in cultured hippocampal neurons. Thus, a composition comprising a pharmaceutically-acceptable carrier, such as sterile saline, and an adenovirus comprising an NMDAR gene, would have been obvious to one of skill in the art at the time of the invention, particularly given that methods for transducing rat brain cells with recombinant adenovirus were well known in the art at the time of the invention as evidenced by Kammesheidt. One of ordinary skill in the art would have anticipated a reasonable expectation of success because a recombinant adenovirus encoding an epitope-tagged NMDA receptor had already been successfully constructed in the prior art as evidenced by Lissin and methods of preparing adenoviral vectors for *in vivo* administration were well known in the art at the time of the invention as evidenced by Kammesheidt.

Therefore, the claimed invention would have been *prima facie* obvious at the time of the invention.

At page 12 of the response, Applicant asserts that Lissin et al. simply describes a reagent that can be used *in vitro* in cell cultures to determine localization to synapses. Applicant further asserts that the NMDA receptor (NR1) of Lissin et al. was epitope-tagged at the amino terminus with a signal sequence followed by a hemaglutinin (HA) epitope tag and that therefore their vector differs from that of the claimed invention. On the contrary, the adenoviral vector of Lissin is identical to the vector recited in the claims. Nothing more is required. The vector of Lissin is in no way excluded from the claimed composition merely by virtue of the epitope tag. Applicant further asserts that there is no suggestion or even a reason to assume that the HA-tagged NR1 described by Lissin et al. can be expressed *in vivo*. This argument has already been addressed in the Office Action of 11/30/06 at page 11. To reiterate, contrary to Applicant's assertion, it is well established that when the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent. See MPEP 2112.01 and *In re Best,* 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989). In the instant case, there is no evidence demonstrating that the claimed products are functionally different than those taught by the prior art.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632